Global Regulatory Policy

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
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RE: Docket No. 2004D-0118: International Conference on Harmonisation; Draft Guidance on Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

Merck & Co., Inc is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally

Merck has participated with health authorities from around the globe in the harmonization of regulatory standards under the auspices of the International Conference on Harmonisation (ICH). The objectives of ICH have been to identify and correct unnecessary redundancies and time-consuming inefficiencies in development of pharmaceutical products caused by incompatible regulatory schemes. We continue to monitor the equitable and consistent application of these harmonized standards to product development and manufacture in order to ensure that new or improved therapies reach patients as swiftly as possible.

For these reasons, we are both interested and qualified to comment on the guidance, "ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process" dated November 13, 2003 and announced in the Federal Register of March 30, 2004.[1]

General Comments

While we fully support development of this ICH chapter, we are aware of another draft guidance document FDA has recently issued on this topic. On September 5, 2003, draft Guidance for Industry entitled, *Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing and Controls Information,* was released for comment.

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[1] 69 FR 16580

We have attempted to compare these two documents for potential inconsistencies and would encourage FDA to utilize its perspective in providing alignment between the two draft documents.

Additionally, we request that FDA consider addition of the following clarifying statement to section 1.1 (Objectives of the Guideline): "*The document provides for a science-based approach to comparability and does not proscribe any one particular analytical, non-clinical or clinical strategy. As such, the use of the word "might" throughout the document provides the manufacturer with the flexibility to employ a science-based approach to its comparability strategy.*" The addition of this statement will support the case-by-case basis for the determination of the comparability strategy for different products.

We suggest that the General Principles, Section 1.4, be expanded to include the following or similar language as helpful guidance to the manufacturer: "Characterization testing of the pivotal clinical material may provide a valuable benchmark to which future lots are bridged following process changes. It would be valuable to perform characterization testing on these pivotal lots to help establish that benchmark, when applicable."

It would be useful to state (Section 2.1: Considerations for the Comparability Exercise) that there is a *hierarchy* of testing schemes utilized to assess comparability. For minor changes, standard release testing may be sufficient. If more data are required to evaluate the change, the standard tests may be augmented by characterization assays or stability testing. Non-clinical and/or clinical studies may augment analytical characterization testing.

Specific Comments

1. Section 1.3 (Scope) states: the *principles adopted and explained in this document apply to: proteins and polypeptides, their derivatives, and products of which they are components (e.g. conjugates)*... Many similar guidelines specifically include or exclude vaccines from their scope. It is not clear if vaccines (conventional, conjugated, and recombinant) are included in the scope of this document. We request that all vaccines be included in the scope of this document.

2. Section 1.4 (General Principles) lines 63 – 65 state: "*If a manufacturer can provide assurance of comparability through analytical studies alone, non-clinical or clinical studies with the post-change product might not be warranted*". Replace "*might not*" with "*are not*". If comparability can be assured through analytical characterization, non-clinical and clinical studies are not warranted.

3. Section 1.4 (General Principles) lines 70 - 71 state: "*To identify the impact of a manufacturing process change, a careful evaluation of all potential consequences on the product, not just the obvious, should be performed.*" Delete "*all*" and "*not just the obvious*" as these terms make the statement vague.

4. Section 1.4 (General Principles) lines 73 - 76 state: "*Quality data on the pre- and post-change products are generated, and a comparison is performed that integrates and evaluates all data available, e.g., characterisation, routine batch analyses, stability, in-process control, and process validation/evaluation data*". As noted previously, comparability testing may be considered a hierarchy of analytical, pre-clinical and clinical testing. As such, we request that "if appropriate" be added following the word characterization in the above sentence.

5. Section 1.4 (General Principles) lines 84 – 86 state: "*Although the products appear highly similar, there is doubt concerning the capability of the analytical procedures to discern relevant differences that can impact the safety and efficacy of the product*". We request revision of the statement to the following in order to be less vague "Although the products appear highly similar, the analytical procedures are not sufficient to discern the relevant differences that can impact the safety and efficacy of the product".

6. Section 1.4 (General Principles) lines 86 – 87 state: "*The manufacturer should consider performing additional nonclinical and/or clinical studies.*" We request the statement be revised to the following: "The manufacturer should consider performing additional biochemical characterization studies. If these are still not sufficient, the manufacturer should consider performing non-clinical or clinical studies, as appropriate." The option for additional analytical characterization should be available before considering clinical and non-clinical studies.

7. Section 2.1 (Considerations for the Comparability Exercise) lines 108 – 111 state: "*Therefore, it might be appropriate to collect data on the drug product to support the determination of comparability even though all process changes occurred in the manufacture of the drug substance*". We are requesting the following revision to this statement: "If there is evidence to indicate the change may impact the performance of subsequent (downstream) process steps, or the quality of the next intermediate or the final product, it may be appropriate to collect data on the intermediate or drug product to support the determination of comparability, even though the process change occurred in the drug substance." Process changes should be evaluated at the process stage where any potential affects can be best characterized.

8. Section 2.2.1 (Analytical Techniques) lines 179 – 185 refer to evaluation of the need to develop additional characterization tests or add new specifications (release tests) We recommend the deletion of the phrase, "*or to establish routine specifications*" because the development of new analytical methods for release is outside the scope of this document.

9. Section 2.2.1 (Analytical Techniques) lines 186 – 189 state: "*The measurement of quality attributes does not necessarily entail the use of validated assays but the assays should be scientifically sound and provide results that are reliable. Those methods used for batch release should be validated in accordance with ICH guidelines (ICH Q2A, Q2B, Q5C, Q6B), as appropriate*". We are requesting revision of this text to read as follows: "Characterisation does not necessarily entail the use of validated assays, but the assays should be scientifically

sound and provide results that are reliable. Those methods used to measure quality attributes for batch release should be validated in accordance with ICH guidelines (ICH Q2A, Q2B, Q5C, Q6B), as appropriate." Methods used to characterize the product may not always be validated. However, quality attributes are those parameters one measures to release the product, or to qualify that the critical attributes of the product have not changed. These methods should be validated.

10. Section 2.2.2: (Characterisation) lines 199 – 202 state: "*When process changes result in a product characterisation profile that differs from that observed in the material used during nonclinical and clinical studies or other appropriate representative materials, the significance of these alterations should be evaluated*". We are requesting a slight revision to this statement to add the text "For example" at the beginning of this statement. This line is antecedent to the previous statement, and serves as an example of when additional characterization may be necessary. Adding "For example" helps to clarify that additional characterization is not always warranted.

11. Section 2.2.2 (Characterisation) lines 249 – 253 state: "*Where the change results in the appearance of new impurities, it might be appropriate to characterise the new impurities, and in some cases, to conduct appropriate nonclinical or clinical studies to confirm that there is no adverse impact on safety or efficacy of the drug product*". We are requesting this statement be revised to the following ", "Where change results in the appearance of new impurities, the new impurities should be identified and characterized, when possible. Depending on the impurity type and amount, non-clinical and/or clinical studies may be necessary to confirm that there is no adverse impact on safety or efficacy of the drug product." New impurities should be identified when possible.

12. Section 2.2.2 (Characterisation) lines 254 – 256 state "*Contaminants should be strictly avoided and/or suitably controlled with appropriate in-process acceptance criteria or action limits for drug substance or drug product*". We suggest elimination of this text as contamination should always be avoided as a principle of general cGMP; but this is not specific to comparability guidance.

13. Section 2.2.3 (Specifications) lines 258 -261 state: "*The tests and analytical procedures chosen to define drug substance or drug product specifications alone are generally not considered adequate to assess the impact of manufacturing process changes since they are chosen to confirm the routine quality of the product rather than to fully characterise it*". We suggest deletion of this text, as often, simple process changes can be adequately characterized by conformance to specifications used for routine release tests. The decision on how much characterization work is necessary to characterize the post-change product should be based on the nature and extent of changes made to the process.

14. Section 2.2.4 (Stability) lines 278 – 280 state "*For many manufacturing process changes even slight modifications of the production procedures, including those made early in the manufacturing process for the drug substance, might cause changes in the stability of the*

post-change product". We suggest rewording this statement because, as written, it may imply that stability data may need to be generated for all process changes, even minor modifications. We recommend more general introductory language, such as, "Certain manufacturing process changes may cause changes in the stability with post change products."

15. Section 2.2.4 (Stability) lines 280 – 284 state: "*Any change with the potential to alter protein structure or purity and impurity profiles should be evaluated for its impact on stability, since proteins are frequently sensitive to changes, such as those to buffer composition, processing and holding conditions, and use of organic solvents*". We suggest deleting the phrase, "...since proteins are frequently sensitive to changes such as those in processing and holding conditions, and use of organic solvents." Changes with the potential to alter protein structure should be evaluated for stability. However, listing these few items implies that stability must always be generated for these types of changes. A change in buffer composition during processing does not always warrant stability studies. Whereas a change to the buffer composition in which the product is held for a period of time may require stability studies.

16. Section 2.3 (Manufacturing Process Considerations) lines 317 – 318 state: "*The rationale for excluding parts of the process from this consideration should be justified*". We suggest deletion of this statement. When minor changes are made to the upstream process, or where changes made to the upstream process can be fully evaluated and characterized at the drug substance process stage, a formal justification for not evaluating in-process controls at the downstream process steps is unwarranted. Additionally, this statement is in conflict with the statement on lines 342-345 which states "*Typically, re-evaluation/re-validation activities for a simple change might be limited to the affected process step, if there is no evidence to indicate that there is impact on the performance of subsequent (downstream) process steps, or on the quality of the intermediates resulting from the subsequent steps*".

17. Section 2.4 (Demonstration of Comparability during Development) lines 387 – 389 state: "*It should be recognised that during development, analytical procedures might not be validated, but should always be scientifically sound and provide results that are reliable and reproducible*". While not all methods are validated at the early stages of development, it is important to validate the potency assay to measure product dose and qualify samples in relevant safety assays, such as sterility.

Conclusion

The assessment of comparability is increasingly recognized as an essential tool when evaluating product characteristics following process changes made during development and those changes to the process post-licensure. Global harmonization of the principles for determining comparability is important to assure effective resource utilization in the generation, analysis and presentation of the data verifying comparability. Additionally, with an agreed upon testing scheme, the regulatory reporting category for these process changes

may be decreased when acceptable comparability is demonstrated. This guideline, when finalized, will be an important reference for sponsors and regulatory agencies alike.

We appreciate the opportunity to share our comments with respect to ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. Please do not hesitate to contact me, should you have any questions.

Sincerely,

Thomas H. Vassall

for Donald M. Black, MD, MBA
Vice President
Global Regulatory Policy